REMARKS/ARGUMENTS

By this Amendment, claims 2, 5-6, 15, 17-25, 35-40, 46-47, 57-68, 76-79, 81, 84-85, 87 canceled, claims 1, 10, 16, 88, 89, 93-95 are amended. Claims 1, 3-4, 7-14, 16, 26-34, 41-45, 48-56, 69-73, 75, 80, 82-83, 86, 88-101 are pending.

Citations to the Specification are directed to U.S. Patent Application Publication No. 2005/0085417.

Support for the amendments to the claims can be found throughout the Specification as filed, and specifically: support for the amendment to claims 1 and 88 for a diagnostic or therapeutic moiety covalently conjugated to at least one targeting moiety that selectively binds to a cell surface receptor can be found in ¶[0047]; support for the limitation in claims 1 and 88 for a spacer moiety of from about 10Å to about 30Å can be found in ¶[0155]; support for the amendment to claim 16 for the limitation Fe(III), Eu(III), can be found in ¶[0065];

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Rejection under 35 USC § 103

Claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, 88-92 and 93-101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al. (US Patent No. 5,714,166), in view of both Meade et al. (US Patent No. 6,713,046) and Basu et al. (Bioconjugate Chem, 1997,8: 481-488).

The Examiner argues that Tomalia et al. teach a compound with the formula X-L1-T, wherein T can be a single-stranded nucleic acid, and that Tomalia et al. teach that the targeting moiety can be used to deliver the therapeutic moiety to a gene within the cell, i.e., antisense DNA, and concludes that Tomalia et al. teach covalently binding nucleic acids to their dendrimers, wherein the nucleic acids can be used to deliver the therapeutic/diagnostic moiety to a specific target inside the cell. The Examiner admits that it does not specifically teach PNA, however, the Examiner argues that Basu et al. teach the advantages of using PNAs as compared to antisense DNA, and also teach conjugating the PNA with a peptide analog of insulin-like growth factor 1 for increased cellular uptake of the PNA, wherein the PNA and the peptide analog are covalently linked by a $(Gly)_4$ linker (Final Office Action at pages 6-7). The Examiner

argues that Tomalia et al. teach covalently binding nucleic acids to their dendrimers, wherein the nucleic acids can be used to deliver the therapeutic/diagnostic moiety to a specific target inside the cell, and concludes that one of skill in the art would have known to replace the antisense DNA of Tomalia et al. with a PNA-peptide of Basu et al. The Examiner argues that by doing such, one of skill in the art would have obtained a compound having the formula X-L1-P-L2-T (Final Office Action at page 7).

However, Tomalia et al. do not teach or suggest compound comprising a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, wherein the PNA comprises a base sequence that is complementary to a target nucleic acid sequence, or pharmaceutically acceptable salts thereof, provided that the compound is represented by a formula X-L1-P-L2-T or pharmaceutically acceptable salts thereof, wherein L1 and L2 represent at least one spacer moiety of from about 10Å to about 30Å, provided that L1 is covalently bound to X and P and L2 is covalently bound to P and T.

Tomalia et al. specifically restricted "genetic materials" (which include PNA) as belonging to a class for which "formation of the complex does not take place via covalent bonding" ('166 Tomalia at column 47, lines 55-62). The other recitations of the (T)e*(P)x*(M)y structure ('166 Tomalia at column 2, lines 53-65, column 16, lines 31-52, column 22, lines 15-35, column 47, lines 1-10, column 52, lines 57-60) do not teach that M represents a PNA. At no point in the 5,714,166 patent do Tomalia et al. state that PNA, or any genetic material, can be covalently bonded to a dendrimer, not in the claims, not in the background, not in the examples. Therefore, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

The Examiner argues that the claims do not require a covalent bond to form X (i.e., attaching the therapeutic material to the dendrimer via a covalent bond) (Final Office Action at page 8). However, claims 1 and 88 specifically require that L1 is covalently bound to X. Covalent bonding of L1 to X is tested in the present application by mass spectroscopy (see Specification at ¶[0066] and ¶[0181]; see also Tian, et al. (2004) Journal of Nuclear Medicine 45(12):2070-2082; Chakrabarti, et al. (2007) Cancer Biology & Therapy 6(6):948-956; Tian, et al. (2007) Journal of Nuclear Medicine 48(10):1699-1707, all cited in the IDS submitted 05-14-

2007). Mass spectroscopic analyses consistently revealed covalent bonding, because the measured masses of the complete, purified probes agreed with the calculated masses. It is a fundamental chemical fact that without such covalent bonding, the calculated and measured masses could not agree with each other.

Furthermore, Tomalia et al. actually teach a compound with the formula (T)e*(P)x*(M)y (column 16, lines 37-52), (column 18, lines 23-67), (column 19, lines 1-67), (column 20, lines 1-29), (column 22, lines 20-26), wherein M represents a diagnostic or therapeutic agent, such as a radionuclide, T represents a target director, such as a moiety that can bind a cell-surface molecule, or a PNA that can bind a nucleic acid, P represents a dendrimer, and wherein M and T are associated with P via identical or different bonds, *. In contrast, the instant claims are directed to a compound X-L1-P-L2-T, wherein X represents a diagnostic or therapeutic agent, such as a radionuclide chelated to a dendrimer (comparable to P*M in Tomalia et al.), P represents a PNA that can bind a nucleic acid (comparable to T in Tomalia et al.), and T represents a cell surface target director, such as a moiety that can bind a cell-surface molecule (comparable to T in Tomalia et al.), and wherein X, P and T are associated with identical or different spacers L1 and L2 to prevent steric hindrance. The L1 and L2 spacers are a non-obvious solution, not taught or suggested by Tomalia et al., or the combination of the references, to the problem of steric hindrance between the three functional units of the claimed compound. In addition, the claims are directed to spacers of from 10Å – 30Å, which is not taught or suggested in the Tomalia reference. This deficiency is not cured by the Basu or Meade references.

Basu et al. reported a construct of the form P-L2-T designed to bind to a specific cellular receptor, internalize to the cytoplasm, and bind to its specific target mRNA. The construct as disclosed in the Basu reference does not contain a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, and does not contain a spacer L1. One skilled in the art would therefore not have been motivated by Basu, et al. to covalently bond X-L1 to P-L2-T. Additionally, as noted above, Tomalia et al. teach away from covalent bonding of genetic materials to dendrimers.

In addition, the claims are directed to a compound comprising a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, wherein the PNA comprises a base sequence that is complementary to a target nucleic acid sequence, or pharmaceutically acceptable salts thereof. While the Basu reference discloses an IGF1 moiety, there is no teaching or suggestion of a diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T) that selectively binds to a cell surface receptor, nor is a therapeutic or diagnostic moiety taught or suggested in the Meade reference. The relevance of Basu et al. to the present application only becomes apparent after the X-L1-P-L2-T has been stated.

The secondary references Meade and Basu do not remedy the aforementioned deficiency of the primary reference, the Tomalia et al. patent, to teach or suggest all the limitations of the claims because Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Moreover, it would not be obvious to a person skilled in the art to modify the teachings of Tomalia with Meade and Basu to reach all the limitations of the claims, for the reasons set forth in the Declaration of Dr. Eric Wickstrom.

DECLARATION

Applicant relies upon **unexpected results** as shown in the Declaration under 37 CFR § 1.132 of Dr. Eric Wickstrom, submitted December 19, 2007. The Federal Circuit has held that if a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900 (Fed. Cir. 1984), MPEP 2143.01. Here, the Examiner attempts to argue that Tomalia can be modified with the Meade and Basu patents to teach or suggest the claimed invention.

However, this modification would be unsatisfactory for its intended purpose, as demonstrated by the unsuccessful attempt by Applicant to synthesize a functional compound as claimed using the teachings or suggestions of Tomalia. In fact, Applicant had to completely alter the approach to synthesize the instantly claimed compound (Declaration at paragraphs 13-17). Here, if the proposed modification or combination of the prior art would change the principle of

operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. See In re Ratti, 270 F.2d 810 (CCPA 1959). This is shown here.

With regard to the Declaration, the Examiner also argues that the Specification teaches that dendrimers can be prepared such that they have reactive groups capable of being attached to a variety of compounds including PNA and linkers and that techniques of attaching PNA to the dendrimers are within the skill in the art and concludes that the Declaration is not consistent with the teachings in the specification. (Final Office Action at page 8). However, as shown in the Declaration, Applicants' attempt to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, as in the In re Ratti case, therefore the claims are patentable.

In addition, while obviousness does not require absolute predictability, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, see In re Rinehart, 531 F.2d 1048 (CCPA 1976), MPEP 2143.02. Here, Applicants attempted to use the Tomalia teachings as the basis for reaching the claimed invention, but were unsuccessful, thereby showing that there was no reasonable expectation of success in modifying the Tomalia teachings. Therefore, the evidence provided by Applicant demonstrates that Applicant has attempted to utilize the PAMAM dendrimer according to the teachings of Tomalia, and that this attempt was unsuccessful.

Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, and Basu references. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-31, 34, 41-45, 48, 50, 52, 54-56, 69-73, 75, 80, 83, 86, 88-92 and 93-101 under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 USC § 103

Claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, 88-92 and 93-101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Tomalia et al., taken with both Meade et al. and Basu et al., in further view of Nakano et al. (Molecular

Therapy, 2001,3: 491-499).

The Examiner argues that the rejection is maintained because Tomalia et al, Meade et al, and Basu et al. do teach the claimed invention. However, the Tomalia, Meade and Basu references were addressed above, and the addition of the Nakano et al. reference does not cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising therapeutic or diagnostic moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Tomalia, Meade, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-34, 41-45, 48, 49-52, 54-56, 69-73, 75, 80, 82, 83, 86, 88-92 and 93-101 under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 USC § 103

Claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, 89-92 and 93-95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. (Bioconjugate Chem, 2002, 13: 1176-1180), in view of both Liang et al. (Molecular Therapy, 2000, 3: 236-243, of record) and Basu et al.

The Examiner argues that Lewis et al. and Liang et al. teach a targeting ligand capable of binding to a cell surface molecule. The Examiner states that the argument that the ligand of Liang et al. lacks the specificity provided by the present invention is not found persuasive because specificity is not claimed, and alleges that the claims only specify a targeting moiety capable of binding a cell surface molecule, which the transferrin of Liang et al. does. The Examiner also argues that even if the claims would recite specific delivery, it is noted that Basu et al. teach specific targeting moieties, and therefore, one of skill in the art would have known to use their targeting moiety to achieve delivery to specific cells (Final Office Action at page 11).

However, while the Examiner acknowledged that Lewis et al. "do not teach a targeting moiety capable of binding to a cell surface molecule (claim 1)" (Final Office Action at pages 7 and 8), the Examiner cites the Liang et al. reference to allegedly remedy the deficiency of Lewis et al. to teach the targeting moiety. However, Liang et al. teach construction of a transferrin-PNA conjugate associated with a plasmid DNA vector for the purpose of plasmid DNA vector delivery into cells to effect gene therapy. It is important to note that Liang et al. reported no cellular uptake of the transferrin-PNA:DNA conjugate until the cationic polymer polyethyleneimine (a detergent that facilitates DNA uptake into any cell) associated with a plasmid DNA vector was added (see Liang at page 240, Figure 5 and Figure 6). Liang et al. reported enhanced vector-encoded enzymatic activity in transfected cells if transferrin-PNA was associated with the plasmid DNA vector:polyethyleneimine complex. Therefore, Liang et al. provide no motivation toward the design of the present diagnostic compound without the concurrent use of polyethyleneimine, which is not a targeting moiety. Furthermore, the toxicity of polyethyleneimine teaches away from utilizing the Liang et al. construct.

The Examiner argues that one of skill in the art would know that the DOTA of Lewis et al. could substitute for polyethyleneimine, since both are known in the art to be efficient at delivery of nucleic acids to the cells (Final Office Action at page 11). Unfortunately, equating DOTA with polyethyleneimine is a serious error. DOTA is a small, negatively charged cyclic molecule designed to bind positively charged metal ions. DOTA has no ability to facilitate DNA uptake into any cell. Polyethyleneimine is a large positively charged detergent polymer that is designed to bind negatively charged polymers, like DNA, for the purpose of creating a neutral particle capable of facile cell penetration.

Lewis et al. teach a DOTA-PNA conjugate designed to target *bcl-2* (i.e., an oncogene), wherein DOTA comprises a chelator for radiometal cations (i.e., a non-polymeric diagnostic moiety) and wherein the PNA, which is 18 bases long, and is further coupled to a detergent-like PTD-4 peptide that facilitates intracellular delivery of the radiolabeled PNA (i.e., a targeting moiety) into any cell. The detergent-like PTD-4 peptide and DOTA are conjugated to PNA via linkers (Abstract, p. 1177, Fig. 1). The Examiner improperly equates a peptide detergent intended for universal intracellular delivery of the radiolabeled PNA (i.e., a membrane

permeating peptide PTD-4) with a specific cell surface receptor targeting moiety of the present invention, which is defined in the specification on page 21, lines 20-21 as "a moiety that comprises any chemical substance that is capable of binding to a cell surface molecule or being bound by a cell surface molecule (e.g., a receptor)." In the instant claims, targeting the conjugate of the invention to a cell surface receptor so that the internalization is achieved via a receptor provides the desired specificity. This specificity cannot be achieved when a general membrane permeating peptide is used instead of a particular cell surface receptor ligand. Therefore, the membrane permeating peptide PTD-4 in Lewis et al. does not constitute a "targeting moiety" as contemplated in this invention.

The Examiner argues that one of skill in the art would have known and would have been motivated to use linkers to attach the targeting and therapeutic moieties to PNA, and that one of skill in the art would have known that, by doing so, functional interference between the PNA and the moieties attached to it would be avoided (Final Office Action at page 12). However, the Examiner erroneously equates a short bifunctional linker, *, intended only to connect the components of (T)e*(P)x*(M)y, with the instantly claimed flexible, hydrophilic spacer, L, 10-30 Å long, in X-L1-P-L2-T, intended to prevent functional interference between the PNA, P, and the moieties, X and T, attached to either end. Such spacers have only been introduced into such PNA constructs by the Applicants. Accordingly, the combination of the references does not teach or suggest all the claim limitations as asserted by the Examiner.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 28-32, 34, 41, 42, 48-52, 69, 71-73, 75, 80, 83, 86, 89-92 and 93-95 under 35 U.S.C. 103(a) is respectfully requested.

Rejection under 35 USC § 103

Claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, 89-92, and 93-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of Nakano et al.

The Examiner argues that the rejection is maintained because ~~over~~ Lewis et al. taken with Liang et al. and Basu et al. do teach the claimed invention. However, the Lewis, Liang, and Basu references were addressed above, and the addition of the Nakano et al. reference does not

cure the deficiency of the combined references to teach or suggest all the limitations of the claims because Nakano, et al. teach multiple intratumoral injections of an adenovirus that overexpresses 347 nucleotides of KRAS RNA to lower translation of KRAS mRNA and slow the growth of colorectal cancer xenografts in mice, as opposed to the compounds comprising targeting moieties as in the instant claims. Further, Nakano, et al. do not teach probes (short oligonucleotide less than 20 nucleotides) binding to specific receptors on cells, probe internalization into cells via receptor, probe release into cellular cytoplasm, or probe binding to mRNA in cellular cytoplasm. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, and Nakano references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 28-34, 41, 42, 48-52, 69, 71-73, 75, 80, 82, 83, 86, 89-92, and 93-95 under 35 U.S.C. 103(a) is respectfully requested.

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Claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, 88-92, and 93-101 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lewis et al. taken with Liang et al. and Basu et al., in further view of both Tomalia et al. and Meade et al.

The Examiner acknowledges Applicant's arguments, but argues that they are not found persuasive, and additionally, the 132 declaration is not sufficient to overcome the instant rejection for the reasons set forth above.

The Examiner admits that Lewis et al., Liang et al., and Basu et al. do not teach a dendrimer or a plurality of chelants optionally complexed to one or more diagnostic metal ions, a biodegradation cleavage site, or intravascular administration (claims 7-14, 16, 26, 27, 43-45, 54-56, and 88), but argues that Tomalia et al. and Meade et al. teach these limitations, and that it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Lewis et al., Liang et al., and Basu et al. according to the teachings of Tomalia et al. and Meade et al., with a reasonable expectation of success.

However, as discussed above, the Lewis, Liang and Basu references do not teach or suggest a conjugate comprising "a polymeric diagnostic or therapeutic moiety (X) covalently conjugated to at least one PNA (P) and covalently conjugated to at least one targeting moiety (T)

that selectively binds to a cell surface receptor", and this deficiency is not cured by the Tomalia or Meade patents, because, as set forth above, as evidenced by the Declaration of Dr. Eric Wickstrom, attempting to use the teachings of Tomalia to reach the claimed invention was unsuccessful, thereby showing that it would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to operate, and Meade et al. do not disclose utilizing PNA covalently bound to a dendrimer and or targeting messenger RNA in a cell. Therefore, all the limitations of the claims are not taught or suggested in the combination of the Lewis, Liang, Basu, Tomalia, and Meade references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1, 3, 4, 7-14, 16, 26-32, 34, 41-45, 48-52, 54-56, 69-73, 80, 83, 86, 88-92, and 93-101 under 35 U.S.C. 103(a) is respectfully requested.

* * *

For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN, COHEN & POKOTILOW, LTD.

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